A stochastic framework for secondary metastatic emission

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Abstract

In this note, we bridge a gap between two descriptions of metastatic growth. The first is a deterministic model introduced by Iwata *et al.* and includes secondary metastatic emission, the other is a stochastic description without secondary metastatic emission. Here we propose a stochastic model with secondary metastatic emission, described in terms of a cascade of Poisson point processes. We show that the Iwata model describes the mean behaviour of our stochastic model. Furthermore, the variation due to the stochasticity of emission is evaluated for published clinical parameters. *To cite this article: N. Hartung, C. Gomez, C. R. Acad. Sci. Paris.*

Résumé

Un cadre stochastique décrivant l'émission métastatique secondaire. Dans cette note, nous faisons le lien entre deux déscriptions de croissance métastatique. Le premier est un modèle déterministe introduit par Iwata *et al.* prenant en compte les émissions métastatiques secondaires, l'autre un modèle stochastique sans émission secondaire. Ici nous proposons un cadre stochastique décrit par une cascade de processus ponctuels de Poisson qui tient compte de l'émission secondaire. Nous montrons que le modèle Iwata décrit le comportement moyen de notre modèle stochastique. De plus, les fluctuations produites par les émissions aléatoires sont évaluées pour un jeu de paramètres cliniques publié. *Pour citer cet article : N. Hartung, C. Gomez, C. R. Acad. Sci. Paris.*

1. Introduction

Metastasis is the extension from a localised cancer to a systemic disease, caused by cancerous cells able to detach from a tumour and to colonise distant tissues. This capacity is acquired through a number of advantageous genetic modifications [5]. Both the selection of a metastatic phenotype and the passage

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from the primary to a secondary site involve randomness and are thus amenable for stochastic modelling. In this note, we will concentrate on the emission rate.

Several authors have proposed to describe metastatic emission by means of a nonhomogeneous Poisson process (e.g. [2,6]), assuming that metastases are emitted independently of one another. Further, they assumed that the emission intensity depended on the tumour size, which has been shown to be linked to the probability of metastatic disease [11]. In these models, metastatic emission by the metastases themselves was neglected. Model predictions have been confronted to data on one patient with multiple bone metastases.

A deterministic model introduced by Iwata *et al.* [9] features a similar dependence of metastatic emission on primary tumour size. In this approach, the size distribution of metastases is modelled by a structured population equation and secondary metastatic emission is taken into account. While model behaviour on short timescales is similar with and without secondary metastatic emission, a considerable divergence has been shown for long-time behaviour [4]. The model accurately reproduced the number and size of metastases in a patient with metastatic liver cancer [9], was fitted to data on the probability of metastatic disease [1] and to kinetic data on the metastatic burden in preclinical experiments [8].

In this note, we bridge the gap between these two approaches by extending the stochastic model to account for secondary emission. Assuming independence of all emission processes, we characterise the expected value and variance of this process using Volterra integral equations. These computations yield the Iwata model as the mean-field equation of the stochastic model with secondary emission. Furthermore, the fluctuations around this model due to random emissions are computed in a clinical scenario.

2. Metastatic models

2.1. *Iwata model*

The evolution of the size-structured metastatic density ρ is described by

$$\begin{aligned}
&X'(t) = g(X(t)), \quad X(0) = 1, \\
&\partial_t \rho(x,t) + \partial_x [g(x)\rho(x,t)] = 0, && (x,t) \in (1,b) \times (0,+\infty), \\
&g(1)\rho(1,t) = \beta(X(t)) + \int_1^b \beta(x)\rho(x,t)dx, && t \in (0,\infty), \\
&\rho(x,0) = 0, && x \in [1,b],
\end{aligned}$$

where

- $X(t)$ is the primary tumour size (in number of cells) at time t, $b = \lim_{t\to+\infty} X(t) \in (1,\infty]$,
- Metastatic growth is described by "transport in size" at a rate $g > 0$
- Metastatic emission is modelled by a non-linear boundary condition: both primary tumour and metastases emit metastases at a rate β depending on their size. Newborn metastases are monocellular.

For small Δx, the expression $\rho(x,t)\Delta x$ may be interpreted as the number of metastases with size between x and $x + \Delta x$. It will be useful to introduce the family of *model observables*

$$F_f(t) = \int_1^b f(x)\rho(x,t)dx,$$

which includes the number of metastases ($f \equiv 1$) and the total metastatic biomass ($f(x) = x$). The following is an equivalent characterisation of the Iwata model in terms of model observables.

Theorem 2.1 (see [7]) *The model observables solve the following renewal equations:*

$$F_f(t) = \int_0^t \beta(X(s)) f(X(t-s)) ds + \int_0^t \beta(X(s)) F_f(t-s) ds.$$

2.2. *Stochastic model without secondary emission*

Reducing the model studied by Hanin and colleagues [2,6] to growth and emission, the number of metastases is described by a nonhomogeneous Poisson process with intensity $\lambda(t) = \beta(X(t))$. More generally, the *model observables* can be defined via a Poisson point process $(T_l)_{l\geq 1}$ with intensity λ (i.e. the arrival times of the Poisson process; see next section for a definition):

$$F_t^{f,1} := \sum_{n\geq 1} \mathbf{1}_{(T_n \leq t)} f\big(X(t-T_n)\big),$$

which, as before includes the number of metastases in the case $f \equiv 1$ and the total biomass with $f(x) = x$. For this process, the expectation and the variance are given by

$$\mathbb{E}(F_t^{f,1}) = \int_0^t f(X(t-s))\lambda(s) ds, \qquad var(F_t^{f,1}) = \int_0^t f(X(t-s))^2 \lambda(s) ds. \tag{1}$$

3. Stochastic model with secondary metastatic emission

3.1. *Formalisation*

Now consider the following situation. In addition to metastatic emission by the primary tumour, each emitted metastasis has the capacity to emit metastases at a rate depending on its size. Secondary emission shall be described by independent nonhomogeneous Poisson processes, that is, a metastasis emitted at time s sheds metastasis with a rate $\lambda(t-s)$ for any $t > s$. In what follows, we describe the model in terms of a cascade of Poisson point processes on $\mathbb{R}^+$ [10].

Definition 3.1 (Poisson Point Process on $\mathbb{R}^+$) *Let Π be a random variable on a probability space $(\Omega, \mathcal{F}, \mathbb{P})$ with values into the set of all countable subsets of $\mathbb{R}^+$. Let us also consider the family $P = (P(A))_{A\in\mathcal{B}(\mathbb{R}^+)}$ defined by*

$$P(A) = Card(\Pi \cap A)$$

for all Borel set $A \in \mathcal{B}(\mathbb{R}^+)$ of $\mathbb{R}^+$. We say that Π is a Poisson point process (PPP) with intensity μ if

(i) for all $A \in \mathcal{B}(\mathbb{R}^+)$, the random variable $P(A)$ has a Poisson distribution with parameter $\mu(A)$,

(ii) for all $n \geq 2$ and disjoint subsets $A_1, \ldots, A_n \in \mathcal{B}(\mathbb{R}^+)$, the random variables $P(A_1), \ldots, P(A_n)$ are independent.

Moreover, P is called the Poisson random measure associated to Π.

Using the basic properties of Poisson random variables and integration with respect to a positive measure we have the following result [3, Chap. 6 p. 251].

Proposition 3.2 *Let Π be a PPP and P the corresponding random measure. We have for $(g,h) \in L^1(\mathbb{R}^+,\mu) \cap L^2(\mathbb{R}^+,\mu)$*

$$\mathbb{E}[P(g)] = \mu(g), \quad \textit{and} \quad \mathbb{E}[P(g)P(h)] = \mu(g)\mu(h) + \mu(gh).$$

Let us remark that the model described in Section 2.2 can be simply expressed as

$$F_t^f = \int_0^t f(X(t-s)) P^{(1)}(ds),$$

where $P^{(1)}$ is the Poisson random measure associated to a PPP denoted by $\Pi^{(1)}$ with intensity $\mu = \lambda(s)ds$. As a result, (1) can be derived directly from Proposition 3.2. The PPP $\Pi^{(1)} = (T^{(1)}_{n_1})_{n_1 \geq 1}$ describes the times for which a metastasis is emitted by the primary tumour. Now, to consider the secondary emission we have to take care of the level in the generational hierarchy (the primary tumour, the metastases emitted from the primary tumour, the metastases emitted from the metastases emitted from the primary tumour, etc.). To this end, let us introduce the cascade of independent PPP on $\mathbb{R}^+$ defined by

$$\big(\Pi^{(k)}_{n_1 \dots n_{k-1}} = (T^{(k)}_{n_1 \dots n_{k-1} n_k})_{n_k \geq 1}, \qquad k \geq 1, \quad \text{and} \quad n_1, \dots, n_k \geq 1\big),$$

where the subscript $n_1 \dots n_{k-1} n_k$ describes the filiation of the metastasis of the k-th generation. Therefore, $\Pi^{(k)}_{n_1 \dots n_{k-1}}$ gives the time it takes for the offspring with filiation $n_1 \dots n_{k-1}$ to give birth to its n_k-th offspring (see Figure 1).

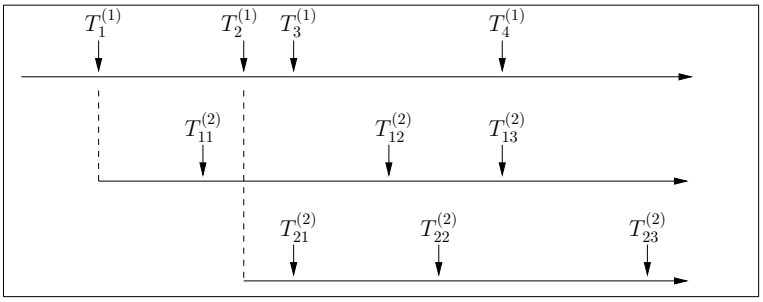

Figure 1. *Illustration of the first two generations in the Poisson point process (PPP) cascade. Each emission event starts a new PPP. Emission times are counted from the start of the respective PPP (and not from zero). / Illustration des deux premières génération de la cascade de processus ponctuels de Poisson (PPP). Chaque évènement d'émission initie un nouveau PPP. Les temps d'émission sont comptés à partir du début du PPP corréspondant (et non de zero).*

Consequently, the observables for the k-th generation can be expressed by

$$F_t^{f,k} = \sum_{n_1, \dots, n_k \geq 1} \mathbf{1}_{\left(\sum_{l=1}^k T^{(l)}_{n_1 \dots, n_l} \leq t\right)} f\Big(X\big(t - \sum_{l=1}^k T^{(l)}_{n_1 \dots, n_l}\big)\Big), \tag{2}$$

and we have the following definition.

Definition 3.3 (Biological observables with secondary emission) *The observables with secondary emission are given by*

$$F_t^f = \sum_{k=1}^{+\infty} F_t^{f,k}.$$

Following the proof of Theorem 3.4 and an iteration procedure, one can show that the observables are well defined since we have

$$\mathbb{E}\Big[|F_t^f|\Big] \leq \|f(X)\|_{L^1(0,t)} \|\lambda\|_{L^\infty(0,t)} e^{t\|\lambda\|_{L^\infty(0,t)}}. \tag{3}$$

A consequence of (2) is that all the observables can be expressed as

$$F_t^f = \sum_{n_1 \geq 1} \mathbf{1}_{(T^{(1)}_{n_1} \leq t)} \Big[f(X(t - T^{(1)}_{n_1})) + G^{f,n_1}_{t - T^{(1)}_{n_1}}\Big] \qquad \text{with} \qquad law(F_t^f) = law(G_t^{f,n_1}) \quad \forall n_1 \geq 1, \tag{4}$$

where $(G_t^{f,n_1})_{n_1 \geq 1}$ are independent, but also independent of $\Pi^{(1)}$. The G_t^{f,n_1} are the contributions coming from the n_1-th offspring of the primary tumour. This expression is very useful to characterise the expectation as well as the variance of the observables.

3.2. *Expectation and variance*

Theorem 3.4 (Expectation of observables) *The expected value $e_f(t) = \mathbb{E}(F_t^f)$ of the observables defined in* (3.3) *satisfies*

$$e_f(t) = \int_0^t \lambda(s) f(X(t-s))ds + \int_0^t \lambda(s) e_f(t-s)ds. \tag{5}$$

Proof. Taking the expectation of (4) and using Proposition 3.2, we have

$$\begin{aligned} e_f(t) &= \mathbb{E}\Big[\int_0^t f(X(t-s))P^{(1)}(ds)\Big] + \mathbb{E}\Big[\sum_{n_1\geq 1} \mathbf{1}_{(T_{n_1}^{(1)}\leq t)} \mathbb{E}\big[G_{t-T_{n_1}^{(1)}}^{f,n_1} \big| \Pi^{(1)}\big]\Big] \\ &= \int_0^t \lambda(s) f(X(t-s))ds + \mathbb{E}\Big[\int_0^t e_f(t-s)P^{(1)}(ds)\Big], \end{aligned}$$

with gives the desired result. □

The observables may also be seen as integrals w.r.t the random measure

$$\mathcal{M}_t := \sum_{k\geq 1} \sum_{n_1,\dots,n_k\geq 1} \delta_{X\left(t-\sum_{l=1}^k T_{n_1\dots,n_l}^{(l)}\right)}.$$

This description permits us to bridge the gap to the Iwata model.

Corollary 3.5 (Link to the Iwata model) *The measure $\mu_t = \mathbb{E}\Big[\mathcal{M}_t\Big]$ is σ-finite, absolutely continuous and its Radon-Nikodým density is given by $\rho(\cdot, t)$, where ρ is the solution of the Iwata model.*

Proof. (3) implies σ-finiteness and absolute continuity of μ_t. Integrating an arbitrary $f \in C^0[1, b]$ w.r.t μ_t, the Radon-Nikodým density is obtained via Theorems 3.4 and 2.1. □

Theorem 3.6 (Variance of observables) *The variance of the observables $v_f(t) = var(F_t^f)$ satisfies*

$$v_f(t) = \int_0^t \lambda(s)\big(f(X(t-s)) + e_f(t-s)\big)^2 ds + \int_0^t \lambda(s) v_f(t-s)ds,$$

where e_f is the solution of (5).

Proof. Using (4) and Proposition 3.2, we have

$$\begin{aligned} \mathbb{E}[\big(F_t^f\big)^2] &= \mathbb{E}\Big[\sum_{n_1\geq 1} \mathbf{1}_{(T_{n_1}^{(1)}\leq t)} \mathbb{E}\big[\big(f(X(t-T_{n_1}^{(1)})) + G_{t-T_{n_1}^{(1)}}^{f,n_1}\big)^2 \big| \Pi^{(1)}\big]\Big] \\ &\quad + \mathbb{E}\Big[\sum_{m_1\neq n_1} \mathbf{1}_{(T_{m_1}^{(1)}\leq t)} \mathbf{1}_{(T_{n_1}^{(1)}\leq t)} \mathbb{E}\big[f(X(t-T_{n_1}^{(1)})) + G_{t-T_{n_1}^{(1)}}^{f,n_1} \big| \Pi^{(1)}\big] \mathbb{E}\big[f(X(t-T_{m_1}^{(1)})) + G_{t-T_{m_1}^{(1)}}^{f,m_1} \big| \Pi^{(1)}\big]\Big] \\ &= \mathbb{E}\Big[\int_0^t \big(f(X(t-s)) + e_f(t-s)\big)^2 P^{(1)}(ds)\Big] + \mathbb{E}\Big[\int_0^t \mathbb{E}\Big[(F_u^f)^2\Big]_{|u=t-s} - \big(e_f(t-s)\big)^2 P^{(1)}(ds)\Big] \\ &\quad - \mathbb{E}\Big[\int_0^t \big(f(X(t-s))ds + e_f(t-s)\big)^2 P^{(1)}(ds)\Big] + \mathbb{E}\Big[\Big(\int_0^t f(X(t-s)) + e_f(t-s)P^{(1)}(ds)\Big)^2\Big], \end{aligned}$$

with gives the desired result. □

4. Numerical illustration

With the link established here, we can evaluate the impact of a stochastic emission w.r.t deviations from the Iwata model. We take up the clinical case study conducted by Iwata *et al.* with the number

of metastases of size greater than c as the observable ($f(x) = \mathbf{1}_{x>c}$) and the parametrisation obtained from fitting the data with the Iwata model, i.e. $g(x) = ax\log(b/x)$ and $\beta(x) = mx^{\alpha}$ with $a = 0.00286$ 1/day, $b = 7.3 \cdot 10^{10}$ cells, $m = 5.3 \cdot 10^{-8}$ 1/(day $\cdot$ cells$^{\alpha}$) and $\alpha = 0.663$. We stress that no information on variability has been used for determining these parameters. The standard deviation of our stochastic model parametrised as above is taken as a measure of variation around the Iwata dynamics. The deviations of the data from mean-field behaviour are within the range of fluctuation explainable with stochastic emission (see Figure 2).

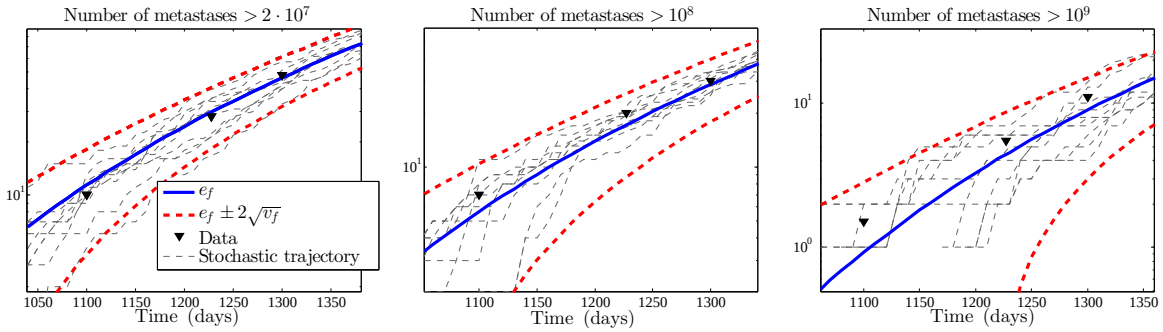

Figure 2. *Comparison of the variability of our stochastic model with the residuals of the clinical data when fitting the Iwata model. / Comparaison de la variabilité de notre modèle stochastique avec les résidus des données cliniques obtenus avec le fit du modèle d'Iwata.*

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